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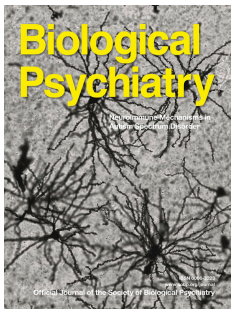

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Abstract

Background: Hippocampal enlargements are commonly reported following electroconvulsive therapy (ECT). To clarify mechanisms, we examined if ECT-induced hippocampal volume change relates to dose (number of ECT sessions and electrode placement) and acts as a biomarker of clinical outcome.

Methods: Longitudinal neuroimaging and clinical data from ten independent sites participating in the Global ECT-MRI Research Collaboration were obtained for mega-analysis. Hippocampal volumes were extracted from structural MR images, acquired before and after patients (*n*=281) experiencing a major depressive episode completed an ECT treatment series using right unilateral (RUL) and bilateral (BL) stimulation. Untreated non-depressed controls (*n*=95) were scanned twice.

Results: The linear component of hippocampal volume change was 0.28%, 0.08 SE, per ECT session, $p<0.001$. Volume change varied by electrode placement in the left (BL: 3.3 ± 2.2%, d=1.5; RUL: 1.6 ± 2.1%, d=0.8; $p<0.0001$), but not the right hippocampus (BL: 3.0 ± 1.7%, d=1.8; RUL: 2.7 ± 2.0%, d=1.4; p=0.36,). Volume change for electrode placement per ECT session varied similarly by hemisphere. Individuals with greater treatment-related volume increases had poorer outcomes (MADRS change -1.0, 0.35 SE, per 1% volume increase, p=0.005), although effects were not significant after controlling for ECT number (slope: -0.69, 0.38 SE, p=0.069).

Conclusions: The number of ECT sessions and electrode placement impacts the extent and laterality of hippocampal enlargement, but volume change is not positively associated with clinical outcome. Results suggest the high efficacy of ECT is not explained by hippocampal enlargement, which alone, might not serve as a viable biomarker for treatment outcome.

Introduction

Major depression is the leading cause of disability worldwide (1), yet standard treatments for depression are only moderately successful (2). There is thus a need to better understand the mechanisms of successful response to antidepressant therapies, which may then inform more effective treatment interventions for patients with major depression. Though depression is typically treated with different forms of psycho- or pharmacotherapies, electroconvulsive therapy (ECT) is still regarded as the most effective acute treatment for severe and treatment resistant major depressive episodes (3). With ECT, electrical current is applied through scalp electrodes, intentionally inducing a seizure, typically 2-3 times per week. When administered with modern techniques under anesthesia, ECT is well tolerated and has a good safety record. Yet, despite its safety and efficacy (3), the neurobiological underpinnings of ECT response, as with other forms of antidepressant treatment, remain unclear. Establishing objective biomarkers of clinical response could allow for the timely implementation of alternative treatment strategies in unresponsive patients.

Most neuroimaging studies of ECT demonstrate treatment-related volume increase of the hippocampus (4-9), which suggests that hippocampal volume may serve as a biomarker of clinical response. These observations together with data from preclinical studies are taken as evidence to support the neurogenic theory of depression (10). In particular, translational models provide evidence to suggest that a decrease of adult neurogenesis in the hippocampus is associated with depression and can potentially be reversed with ECT (10-12). This hypothesis is supported by observations that the human hippocampus harbors neuronal stem cells that

proliferate throughout life (13), that the volume of the hippocampus is frequently reported as reduced in depression (14), and that in an animal model of ECT, a dose-dependent increase in neurogenesis is seen (15). However, the mechanisms underlying ECT-related volume enlargement of the human hippocampus remain unclear, and associations with clinical outcome have not been demonstrated conclusively (9).

In ECT practice, the number of treatments in an ECT index series typically depends on severity of depression and the speed of recovery, such that unresponsive patients tend to receive more ECT sessions on average (16). Bilateral (BL) electrode placement is widely used for stimulation. However, to mitigate risk for cognitive side effects, particularly for verbal and retrograde autobiographical memory, the use of other electrode montages are also standard practice (17-19). In particular, right unilateral (RUL) ECT, which was developed in an effort to reduce the spread of seizure activity to brain areas such as left temporal cortex important for verbal memory, is often used as a first line form of ECT (17, 18). Computational modelling of electric fields supports that bilateral ECT leads to more diffuse brain stimulation than more focal RUL ECT (20, 21). Both the number of ECT sessions received and electrode placement may thus impact the extent and laterality of hippocampal neuroplasticity and in turn the mechanisms of treatment response. However, prior studies have lacked the sample sizes and statistical power needed to investigate the moderating effects of these parameters, or have simply controlled for these factors as nuisance variables. Consequently, no clear associations between dose or mode of electrode placement and measured hippocampal structural changes have emerged (12, 22, 23).

To address the clinical relevance of ECT-related hippocampal volume change, we included 281 patients from the Global ECT-MRI Research Collaboration (GEMRIC) (24), and analyzed volume changes of the hippocampus after serial ECT treatment. With the largest and most geographically diverse sample to date, and by using an optimized image processing pipeline, we obtained sufficient statistical power to probe for relationships between hippocampal volume, dose response (number of sessions as well as electrode placement) and symptom improvement of relatively small effects (24) ($f2$ = 0.03, α=.05, Power=.80, as estimated for a linear model with 1,280 degrees of freedom). Changes in hippocampal volume in untreated non-depressed controls scanned at two different time points were also assessed to estimate the variance associated with repeated measures over time.

Methods and Materials

Participants. The clinical and demographic characteristics of the GEMRIC sample are summarized in Table 1, as also detailed in (24). Data from 10 sites were available, including n=281 patients (59.8% female, age 54.8 ± 16.4) and n=95 healthy controls (60% female, age 46.9 ± 14.6). Patients were scanned before and after ECT, and controls were scanned at two time points without receiving ECT. Due to some missing data points (e.g. follow up scan, number of ECTs, or depression score), the sample sizes for the statistical models used to test for the effects of ECT number or relationships with clinical outcome ranged from 250 to 268 patient participants. ECT practice varied among contributing sites in terms of electrode placement and/or stimulation parameters as detailed previously (24). Concurrent psychotropic medications were used at most sites, as describe in Supplemental information. To test for the effects of electrode placement, only patients that received exclusively RUL (n=149) or BL (n=50; 10 bifrontal (BF), 40 bitemporal (BT)) treatment throughout all sessions of the ECT index series were included for analysis. All sites contributing data received approval by their local ethical committees or Institutional Review Board, and the centralized mega-analysis was approved by the Regional Ethic Committee South-East in Norway (2013/1032 ECT and Neuroradiology, June 1st 2015).

Image acquisition and post processing. The image processing methods have been detailed previously (24). Briefly, T1-weighted MRI volumes with a minimal resolution of 1.3 mm in any direction were acquired before and after (typically within 1-2 weeks) an ECT treatment series using 1.5T (1 site) or 3T (9 sites) scanners. Raw structural MRI data from each site were uploaded to a common server and

were analyzed together using the same preprocessing steps. During preprocessing, images were corrected for scanner specific gradient non-linearity (25), registered to a common atlas space and resampled to an isotropic 1 mm^3 spatial resolution. Further processing was performed by FreeSurfer version 5.3, and Quarc (26) was used for unbiased estimation of hippocampal volume change. The automated segmentation of FreeSurfer for hippocampal volume measurement has been shown to be comparable to results from manual tracings (27-29). Depressive symptoms were rated by the Montgomery-Åsberg Depression Rating Scale (MADRS). For sites collecting only the 17- or 24-item Hamilton Depression Rating Scale (HAM-D), a validated equation was used to convert HAM-D-17 to MADRS scores (30).

For all modes of electrode placement employed across sites, one of the electrodes was placed over the right (non-dominant) hemisphere, hence the right hippocampus was chosen for primary analysis to determine dose effects of repeated ECT treatments and relationships with clinical response, weighting ECT session similarly regardless of participant variations for electrode placement within or across sites. The same effects were examined for the left hippocampus and results from these analyses are provided in the Supplement. Follow-up analyses were performed to examine the effects of BL and RUL electrode placement on both the right and left hippocampus, excluding one patient that received left anterior right temporal (LART) and patients who received a combination of RUL and BL during the index series. Quality control of hippocampal segmentation was performed by procedures adapted from the ENIGMA consortium (http://enigma.usc.edu/) (31).

Statistical analysis. Statistical analysis was performed with the R software

package, version 3.3.1 (32). Slopes from linear models are reported with ± Standard Error (SE) and all other results are reported as Mean ± Standard Deviation (SD). Primary analyses addressed relationships between 1) the number of ECT sessions and hippocampal volume change, and 2) hippocampal volume change and change in MADRS score pre to post ECT using the General Linear Model (GLM). In a subsample of patients receiving only BL or RUL ECT, effects of electrode placement were additionally examined, and differences in slopes were tested using the function linearHypothesis in R (car-package, version 2.1-6). To control for and evaluate non-linear effects, the number of ECT sessions squared was included as a covariate. To control for Age, Sex, Site, baseline hippocampal volume and baseline depression score, these variables were included as covariates in the models as specified in the Results. Considering our *a priori* hypotheses and the large amount of literature showing changes in hippocampal volume with ECT (9), individual tests were considered significant at a level of $p < 0.01$, corresponding to a Bonferroni correction for 5 independent hypotheses. In the results figures, the regression lines (with 95% confidence intervals shown as shaded areas) represent the relationships between dependent and independent variables calculated without covariates. Cohen´s *d* for volume change was calculated as mean change/SD. Finally, relationships between volume change and number of ECT sessions were additionally examined in responders (patients who showed >50% change in MADRS score over the course of ECT, n = 150) versus non-responders (n = 98) using Welch Two Sample *t*-tests (two-sided).

Results

First, we tested whether volume change of the hippocampus is positively associated with number of ECT sessions over time, including number of ECTs squared (to estimate non-linear effects), Age, Sex, Site, baseline depression score, and baseline hippocampal volume as covariates. For the right hippocampus, we found that the linear component (slope) of volume change (%) versus number of ECTs was 0.28 ± 0.083, (t(225) = 3.35, $p < 0.001$). The square term was near significant -0.0048 ± 0.002, (t(225) = -1.94, $p = 0.053$), suggesting a sub-linear relationship (Figure 1A) that reflects larger volume changes occur early in the ECT treatment series. When comparing control subjects scanned at two distinct time points, no significant changes in hippocampal volume were observed; mean 0.05 % ± 0.08, $d = 0.06$, n = 95; $p = 0.54$ (One Sample *t*-test). Results for the left hippocampus, which are presented in the Supplement, showed similarly significant volume enlargement with increasing number of ECT sessions. Mean volumes are provided in Table 1.

Next, we tested whether clinical outcome following ECT, measured using the MADRS, is positively associated with change in right hippocampal volume, when controlling for effects of Age, Sex, Site, baseline depression score and baseline hippocampal volume. Contrary to our hypothesis that patients with greater clinical response would exhibit larger volume increases, we found a negative relationship (slope -1.0 ± 0.35, t(233) = -2.84, $p < 0.005$) (Figure 1B) indicating less change in those with the greatest improvement. Separating patients based on the extent of clinical response over the course of ECT, volume change (%) was 2.6 ± 2.0, $d = 1.3$ and 3.3 ± 1.7, $d = 1.9$ for responders (those with > 50% improvement in mood scores) and non-responders, respectively ($p = 0.009$, Figure 1C). However, we also

observed that the number of ECT sessions was associated with worse outcome (Figure 1D and see Supplemental information) such that non-responders were prescribed and received more sessions than responders (13.2 ± 4.7 versus 11.5 ± 5.3, t(232.11) = 2.74, p = 0.007). Thus, to control for differences in the length of treatment for responsive versus non-responsive patients, the number of ECT sessions was additionally included as covariate to the model addressing the relationship between change in hippocampal volume and change in mood rating. When additionally controlling for the number of ECT sessions, the slope of change in MADRS score versus volume change remained negative, but was no longer significant (-0.69 ± 0.38, t(225) = -1.83, p = 0.069). The effect size of hippocampal volume change (partial eta squared) was 0.03 and 0.01 before and after adding number of ECT sessions as a covariate. As shown in the Supplement, positive relationships between left hippocampal volume enlargement and clinical change were also absent. Follow-up analyses examining effects of ECT number and relationships with clinical outcome in ECT responders and non-responders for both the left and right hippocampus are also presented in the Supplemental information (see Figure S1).

Finally, to investigate the effects electrode placement, we constructed separate linear models for change in volume for the right and left hippocampus with separate slopes for the number of RUL or BL ECT sessions, controlling for Age, Sex, Site, baseline depression score and baseline hippocampal volume. For the right hippocampus (Figure 2A), the slopes of volume change per ECT session for RUL and BL electrode placement were both ~0.13, suggesting similar effects for number of BL and RUL treatments. Change in volume (mean ± SD) was also similar for BL

and RUL electrode placement, 3.0 ± 1.7%, d = 1.8 and 2.7 ± 2.0%, d = 1.4, p = 0.36, *t*-test, respectively. For the left hippocampus (Figure 2B), the slope of volume change (slope ± SE) versus number of treatments was steeper for BL (0.18 ± 0.03, $p = 1.9 \times 10^{-7}$) than RUL (0.06 ± 0.04, $p = 0.15$) electrode placements ($p = 0.007$, Linear hypothesis test). Change in left hippocampal volume was also greater for BL with respect to RUL stimulation (BL: 3.3 ± 2.2%, $d = 1.5$; RUL: 1.6 ± 2.1%, $d = 0.8$, p $= 1.5 \times 10^{-5}$, *t*-test). The effect of electrode placement on the left hippocampal volume change was further confirmed by a number of ECTs-by-electrode placement interaction ($p = 0.007$) in a model of left hippocampal volume change versus number of ECTs where electrode placement was included as a separate covariate (see Supplemental Information, Model 2c).

Discussion

Including the largest sample of patients with ECT studied with neuroimaging methods to date, our findings showed a highly significant number of ECT session dose-dependent biological effect of ECT on hippocampal volume. We also showed that electrode placement differentially affects the extent of volume change in the right and left hippocampus. Specifically, BL stimulation accounts for similar changes in volume for both the right and left hippocampus, but RUL stimulation lead to more focal effects in the right hippocampus. However, contrary to our expectations, we also found that volume enlargement of the hippocampus is not significantly related to treatment outcome. Instead, results showed a negative relationship between hippocampal volume and symptom improvement such that individuals with greater hippocampal enlargement tend to have less response. However, patients with poor response received more treatments, and this negative relationship was not significant when the number of ECT sessions were taken into account. This finding represents a major deviation from the common assumption in the field of a positive association between ECT-induced volume enlargement and clinical improvement. Rather, results indicate that gross volume increase of the hippocampus by itself is not a meaningful biomarker for positive therapeutic response.

Findings from this study showed that ECT dose parameters including the number of ECT sessions received and the location of electrode placement modulated the magnitude and hemispheric specificity of hippocampal volume change. Here, results demonstrated a clear and dose-dependent effect of number of ECT sessions on hippocampal volume in both the right and left hemispheres. Further, RUL and BL ECT showed differential effects on volume change in the left and right hippocampus.

Existing data supports that the antidepressant efficacy and cognitive side effects of ECT are influenced by electrode position as well as other stimulus parameters (17, 33, 34). Designed to reduce cognitive side effects, with RUL electrode placement, electrical stimulation is focused away from the dominant (left) hemisphere (35). In contrast, the right side of the brain is targeted by both RUL and BL electrode placements. Hence, if the electrical stimulus is modulating the volume change, a clear difference in volumetric effect of RUL versus BL stimulation for the left hippocampus is expected. In line with this hypothesis, and computational modelling results showing more prominent electric field increases in the right hemisphere for RUL ECT and in both hemispheres for BL ECT (20, 21), our results show volume increases are greater in the right hippocampus for RUL, while BL ECT leads to similar volume increases in both hemispheres (Figure 2).

Though we have shown that hippocampal volume enlargement is influenced by ECT dose parameters, the clinical relevance of these changes remains unclear. ECT-induced volume enlargement of the hippocampus (4-8) has led to the suggestion that treatment-related neuroplasticity may underlie symptom improvement (12). From a mechanistic perspective, stress in combination with genetic or epigenetic factors may reduce neurogenesis and precipitate a depressive episode, and antidepressant therapies (such as ECT) might work through restoration of the basal rate of neurogenesis in the hippocampal dentate gyrus (11). Since both left (Figure S1B and D) and right (Figure 1) hippocampal volume change relates to the number of ECT treatments received, but does not positively associate with clinical outcome, enlargement of the hippocampus may be an epiphenomenon of ECT. Overall

enlargement of hippocampal volume observed with ECT may thus relate to seizure therapy itself rather than to the therapeutic effects of treatment.

Our results have important implications for treatment management and raise several questions and challenges relevant to understanding the neurobiological underpinnings of ECT. It is a common experience among ECT-practitioners that the patients with the highest depression scores tend to be the ones with the higher response rates (36), and often these patients respond quickly. At the same time, longer depressive episodes and medication failure at baseline are indicators of poor response to ECT (37). The number of treatments prescribed is typically based on clinically determined response, and patients with modest response are thus more likely to receive a larger number of ECT sessions in the index series (16). However, while the biological effects of ECT may be expected to relate to the number of treatments received, as shown for growth of the hippocampus, there is not an apparent parallel regarding improvement in depression score (Figure 1D).

It is conceivable that several different biological processes impact ECT clinical response and these might or might not overlap with the biological manifestations of seizure therapy itself. Animal studies support that in addition to neurogenesis, multiple other neurophysiological and neuroplastic changes occur following electroconvulsive shock (ECS). Thus, it is possible that particular micro-environmental events may influence the overall macroscopic structure of the hippocampus, while separate or concurrent processes constitute the mechanisms underlying antidepressant response. For example, changes in cellular or synaptic density and intra/extracellular fluid might impact gross changes in hippocampal

volume. Animal models have shown dose-dependent increase in markers of hippocampal neural, glial and endothelial cell proliferation and density following ECS (15, 38-40) that may result in an absolute increase in the number of synapses or specific cell types (41). Notably, a dissociation between neural changes and behavior was reported in a recent animal model study, where ECT was shown to stimulate neurogenesis, but the number of new neurons did not predict the extent of behavioral outcome (42). These results are compatible with our findings with respect to the absence of clinical response relationships. At the same time, hippocampal volume may be influenced by fluid content, which may vary as a consequence of increased vascularization (43) and blood flow (44, 45), or inflammation (46-48) as supported by an observed ECS upregulation of markers for microglia (49, 50).

Other molecular effects, not necessarily independent, may relate more directly to antidepressant response. For example, ECS is also shown to modulate monoaminergic neurotransmission (51), as similar to standard antidepressant treatment. Increased expression of brain-derived neurotrophic factor (BDNF) (52, 53) and vascular endothelial growth factor (VEGF) (54) are also reported with ECS or ECT in humans, and have been linked to changes in behavior (52, 55). Further, ECS elicits a number of hippocampal epigenetic modifications, including GADD45B-dependent DNA demethylation (56), and the alteration of histone and DNA modifying enzymes (57), which may influence structural neuroplasticity at both the macro and micro-scale.

It is also possible that neurogenesis or other neurotrophic or neurophysiological events induced by ECT may precede or lag behind clinical response. Further,

variations in the morphology of different regions of the hippocampus (for example, the dentate gyrus or the anterior hippocampus with more connections to neural circuits associated with mood regulation and emotional behavior) may be more sensitive to ECT outcome. For example, analyses of change in hippocampal shape with ECT have indicated greater regional changes in the right anterior hippocampus (12), as well as changes specific to particular hippocampal subfields (7). A recent study in 24 subjects also suggested that volumes of hippocampal subfields at baseline could predict response to ECT treatment (58), however this finding needs replication in larger samples.

Our study has some limitations, most notably the design is retrospective (e.g. no *a priori* standardization of MR protocols or depression scoring) and assessments were limited to before- and after treatment. Further, the design was naturalistic, so patients who remained unresponsive were prescribed a greater number of ECT sessions on average. Other unknown moderators or speed of response, which can impact clinical decisions regarding the number of treatments prescribed (59), remain similarly unaccounted for. For example, other stimulation parameters such as pulse width and frequency and seizure threshold may also impact neural changes. However, since these parameters varied across sites, including during the ECT treatment series for individual patients, they were not investigated. Animal studies have also shown that both ECS, and to a lesser extent, chronic antidepressant treatment impact neurogenesis in the rat hippocampus (38). It is thus possible that the continuation of psychotropic medication during ECT might impact hippocampal structure. However, follow-up analysis revealed the extent of volume change was

similar for participants tapered off all antidepressants, benzodiazepines and anticonvulsants during ECT (Figure S2).

Cognitive side effects remain a fundamental concern in ECT practice, and were not examined in this study and thus warrant future research. Future studies would also benefit from including repeated assessments at multiple time points throughout treatment to allow examination of the trajectories and speed of change, and explore ways of subgrouping depressed individuals, possibly by identifying biological subtypes (60). Implementing machine-learning approaches, with a goal of identifying individuals that are likely to respond to ECT (61), and investigations using higher resolution imaging approaches to investigate sub-regions of the hippocampus (58) may also advance the field. Another avenue of future research would be studies with standardized ECT protocols across all participants to reduce confounds and increase the power of the designs to identify moderators conclusively. New approaches are needed to identify biomarkers that can explain and predict the clinical effect of ECT, separate from seizure or other procedural effects, which also may inform other antidepressant treatments.

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Anders M. Dale is a Founder of and holds equity in CorTechs Labs, Inc, and serves on its Scientific Advisory Board. He is also a member of the Scientific Advisory Board of Human Longevity, Inc. (HLI), and receives funding through research agreements with General Electric Healthcare (GEHC). The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict of interest policies.

All other authors report no biomedical financial interests or potential conflicts of interest.

Author contributions

LO wrote the first draft and coordinated the work. LO, UK, HB, KJE, OBP, MBJ, CCA and AMD contributed in planning and/or design the project. LO, UK, KJO, VJE, MBJ, LGH, KLN, CCA, AD, MLS, MLO, LE, MV, PS, PvE, IT, MA, RR, TH, UD, AA, RE contributed data. LO, HB, AMD, KLN, AD, MLS, MLO, LE, MV, PS, MA, RR, AA, GH, RE and CCA contributed in processing and/or analysis/interpretation of data. All authors contributed to manuscript revisions and approved of the final version.

References

1. Friedrich MJ (2017): Depression Is the Leading Cause of Disability Around the World. *JAMA*. 317:1517.
2. Insel TR, Wang PS (2009): The STAR*D trial: revealing the need for better treatments. *Psychiatr Serv*. 60:1466-1467.
3. Carney S, Cowen P, Dearness K, Eastaugh J (2003): Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 361:799-808.
4. Nordanskog P, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A (2010): Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J Ect*. 26:62-67.
5. Tendolkar I, van Beek M, van Oostrom I, Mulder M, Janzing J, Voshaar RO, et al. (2013): Electroconvulsive therapy increases hippocampal and amygdala volume in therapy refractory depression: a longitudinal pilot study. *Psychiatry research*. 214:197-203.
6. Dukart J, Regen F, Kherif F, Colla M, Bajbouj M, Heuser I, et al. (2014): Electroconvulsive therapy-induced brain plasticity determines therapeutic outcome in mood disorders. *Proc Natl Acad Sci U S A*. 111:1156-1161.
7. Abbott CC, Jones T, Lemke NT, Gallegos P, McClintock SM, Mayer AR, et al. (2014): Hippocampal structural and functional changes associated with electroconvulsive therapy response. *Translational psychiatry*. 4:e483.
8. Ota M, Noda T, Sato N, Okazaki M, Ishikawa M, Hattori K, et al. (2015): Effect of electroconvulsive therapy on gray matter volume in major depressive disorder. *J Affect Disord*. 186:186-191.
9. Wilkinson S, T., Sanacora G, Bloch MH (2017): Hippocampal Volume Changes Following Electroconvulsive Therapy: A Systematic Review and Meta-analysis. *Biol Psychiatry*. 2:327-335.
10. Miller BR, Hen R (2015): The current state of the neurogenic theory of depression and anxiety. *Curr Opin Neurobiol*. 30:51-58.
11. Jacobs BL, van Praag H, Gage FH (2000): Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry*. 5:262-269.
12. Joshi SH, Espinoza RT, Pirnia T, Shi J, Wang Y, Ayers B, et al. (2016): Structural Plasticity of the Hippocampus and Amygdala Induced by Electroconvulsive Therapy in Major Depression. *Biol Psychiatry*. 79:282-292.
13. Eriksson PS, Perfilieva E, Bjork-Eriksson T, Alborn AM, Nordborg C, Peterson DA, et al. (1998): Neurogenesis in the adult human hippocampus. *Nat Med*. 4:1313-1317.
14. Schmaal L, Veltman DJ, van Erp TG, Samann PG, Frodl T, Jahanshad N, et al. (2016): Subcortical brain alterations in major depressive disorder: findings from the ENIGMA Major Depressive Disorder working group. *Mol Psychiatry*. 21:806-812.
15. Madsen TM, Treschow A, Bengzon J, Bolwig TG, Lindvall O, Tingstrom A (2000): Increased neurogenesis in a model of electroconvulsive therapy. *Biol Psychiatry*. 47:1043-1049.
16. Brus O, Cao Y, Gustafsson E, Hulten M, Landen M, Lundberg J, et al. (2017): Self-assessed remission rates after electroconvulsive therapy of depressive disorders. *Eur Psychiatry*. 45:154-160.

17. Kolshus E, Jelovac A, McLoughlin DM (2017): Bitemporal v. high-dose right unilateral electroconvulsive therapy for depression: a systematic review and meta-analysis of randomized controlled trials. *Psychol Med*. 47:518-530.
18. Radman T, Lisanby SH (2017): New directions in the rational design of electrical and magnetic seizure therapies: individualized Low Amplitude Seizure Therapy (iLAST) and Magnetic Seizure Therapy (MST). *Int Rev Psychiatry*. 29:63-78.
19. Tor PC, Bautovich A, Wang MJ, Martin D, Harvey SB, Loo C (2015): A Systematic Review and Meta-Analysis of Brief Versus Ultrabrief Right Unilateral Electroconvulsive Therapy for Depression. *J Clin Psychiatry*. 76:e1092-1098.
20. Bai S, Galvez V, Dokos S, Martin D, Bikson M, Loo C (2017): Computational models of Bitemporal, Bifrontal and Right Unilateral ECT predict differential stimulation of brain regions associated with efficacy and cognitive side effects. *Eur Psychiatry*. 41:21-29.
21. Deng ZD, Lisanby SH, Peterchev AV (2011): Electric field strength and focality in electroconvulsive therapy and magnetic seizure therapy: a finite element simulation study. *J Neural Eng*. 8:016007.
22. Jorgensen A, Magnusson P, Hanson LG, Kirkegaard T, Benveniste H, Lee H, et al. (2016): Regional brain volumes, diffusivity, and metabolite changes after electroconvulsive therapy for severe depression. *Acta Psychiatr Scand*. 133:154-164.
23. Bouckaert F, Dols A, Emsell L, De Winter FL, Vansteelandt K, Claes L, et al. (2016): Relationship Between Hippocampal Volume, Serum BDNF, and Depression Severity Following Electroconvulsive Therapy in Late-Life Depression. *Neuropsychopharmacology*. 41:2741-2748.
24. Oltedal L, Bartsch H, Sorhaug OJ, Kessler U, Abbott C, Dols A, et al. (2017): The Global ECT-MRI Research Collaboration (GEMRIC): Establishing a multi-site investigation of the neural mechanisms underlying response to electroconvulsive therapy. *Neuroimage Clin*. 14:422-432.
25. Jovicich J, Czanner S, Greve D, Haley E, van der Kouwe A, Gollub R, et al. (2006): Reliability in multi-site structural MRI studies: effects of gradient non-linearity correction on phantom and human data. *NeuroImage*. 30:436-443.
26. Holland D, Dale AM (2011): Nonlinear registration of longitudinal images and measurement of change in regions of interest. *Med Image Anal*. 15:489-497.
27. Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al. (2002): Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. *Neuron*. 33:341-355.
28. Morey RA, Petty CM, Xu Y, Hayes JP, Wagner HR, 2nd, Lewis DV, et al. (2009): A comparison of automated segmentation and manual tracing for quantifying hippocampal and amygdala volumes. *NeuroImage*. 45:855-866.
29. Sanchez-Benavides G, Gomez-Anson B, Sainz A, Vives Y, Delfino M, Pena-Casanova J (2010): Manual validation of FreeSurfer's automated hippocampal segmentation in normal aging, mild cognitive impairment, and Alzheimer Disease subjects. *Psychiatry research*. 181:219-225.
30. Heo M, Murphy CF, Meyers BS (2007): Relationship between the Hamilton Depression Rating Scale and the Montgomery-Asberg Depression Rating Scale in depressed elderly: a meta-analysis. *Am J Geriatr Psychiatry*. 15:899-905.
31. Stein JL, Medland SE, Vasquez AA, Hibar DP, Senstad RE, Winkler AM, et al. (2012): Identification of common variants associated with human hippocampal and intracranial volumes. *Nat Genet*. 44:552-561.

32. R Core Team (2016): R: A language and environment for statistical computing. Vienna, Austria. URL https://www.R-project.org/: R Foundation for Statistical Computing.
33. Spellman T, Peterchev AV, Lisanby SH (2009): Focal electrically administered seizure therapy: a novel form of ECT illustrates the roles of current directionality, polarity, and electrode configuration in seizure induction. *Neuropsychopharmacology*. 34:2002-2010.
34. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. (2000): A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 57:425-434.
35. d'Elia G (1970): Unilateral electroconvulsive therapy. *Acta Psychiatr Scand Suppl*. 215:1-98.
36. Nordenskjold A, von Knorring L, Engstrom I (2012): Predictors of the short-term responder rate of Electroconvulsive therapy in depressive disorders--a population based study. *BMC Psychiatry*. 12:115.
37. Haq AU, Sitzmann AF, Goldman ML, Maixner DF, Mickey BJ (2015): Response of depression to electroconvulsive therapy: a meta-analysis of clinical predictors. *J Clin Psychiatry*. 76:1374-1384.
38. Malberg JE, Eisch AJ, Nestler EJ, Duman RS (2000): Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci*. 20:9104-9110.
39. Perera TD, Coplan JD, Lisanby SH, Lipira CM, Arif M, Carpio C, et al. (2007): Antidepressant-induced neurogenesis in the hippocampus of adult nonhuman primates. *J Neurosci*. 27:4894-4901.
40. Scott BW, Wojtowicz JM, Burnham WM (2000): Neurogenesis in the dentate gyrus of the rat following electroconvulsive shock seizures. *Exp Neurol*. 165:231-236.
41. Chen F, Madsen TM, Wegener G, Nyengaard JR (2009): Repeated electroconvulsive seizures increase the total number of synapses in adult male rat hippocampus. *Eur Neuropsychopharmacol*. 19:329-338.
42. Olesen MV, Wortwein G, Folke J, Pakkenberg B (2017): Electroconvulsive stimulation results in long-term survival of newly generated hippocampal neurons in rats. *Hippocampus*. 27:52-60.
43. Hellsten J, Wennstrom M, Bengzon J, Mohapel P, Tingstrom A (2004): Electroconvulsive seizures induce endothelial cell proliferation in adult rat hippocampus. *Biol Psychiatry*. 55:420-427.
44. Milo TJ, Kaufman GE, Barnes WE, Konopka LM, Crayton JW, Ringelstein JG, et al. (2001): Changes in regional cerebral blood flow after electroconvulsive therapy for depression. *J Ect*. 17:15-21.
45. Takano H, Motohashi N, Uema T, Ogawa K, Ohnishi T, Nishikawa M, et al. (2011): Differences in cerebral blood flow between missed and generalized seizures with electroconvulsive therapy: a positron emission tomographic study. *Epilepsy Res*. 97:225-228.
46. Yrondi A, Sporer M, Peran P, Schmitt L, Arbus C, Sauvaget A (2018): Electroconvulsive therapy, depression, the immune system and inflammation: A systematic review. *Brain Stimul*. 11:29-51.
47. van Buel EM, Patas K, Peters M, Bosker FJ, Eisel UL, Klein HC (2015): Immune and neurotrophin stimulation by electroconvulsive therapy: is some inflammation needed after all? *Translational psychiatry*. 5:e609.
48. Fluitman SB, Heijnen CJ, Denys DA, Nolen WA, Balk FJ, Westenberg HG (2011): Electroconvulsive therapy has acute immunological and neuroendocrine effects in patients with major depressive disorder. *J Affect Disord*. 131:388-392.

49. Jansson L, Wennstrom M, Johanson A, Tingstrom A (2009): Glial cell activation in response to electroconvulsive seizures. *Prog Neuropsychopharmacol Biol Psychiatry*. 33:1119-1128.
50. Wennstrom M, Hellsten J, Tingstrom A (2004): Electroconvulsive seizures induce proliferation of NG2-expressing glial cells in adult rat amygdala. *Biol Psychiatry*. 55:464-471.
51. Baldinger P, Lotan A, Frey R, Kasper S, Lerer B, Lanzenberger R (2014): Neurotransmitters and electroconvulsive therapy. *J Ect*. 30:116-121.
52. Polyakova M, Schroeter ML, Elzinga BM, Holiga S, Schoenknecht P, de Kloet ER, et al. (2015): Brain-Derived Neurotrophic Factor and Antidepressive Effect of Electroconvulsive Therapy: Systematic Review and Meta-Analyses of the Preclinical and Clinical Literature. *PLoS One*. 10:e0141564.
53. Nibuya M, Morinobu S, Duman RS (1995): Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. *J Neurosci*. 15:7539-7547.
54. Warner-Schmidt JL, Madsen TM, Duman RS (2008): Electroconvulsive seizure restores neurogenesis and hippocampus-dependent fear memory after disruption by irradiation. *Eur J Neurosci*. 27:1485-1493.
55. Minelli A, Zanardini R, Abate M, Bortolomasi M, Gennarelli M, Bocchio-Chiavetto L (2011): Vascular Endothelial Growth Factor (VEGF) serum concentration during electroconvulsive therapy (ECT) in treatment resistant depressed patients. *Prog Neuropsychopharmacol Biol Psychiatry*. 35:1322-1325.
56. Jun H, Mohammed Qasim Hussaini S, Cho CH, Welby J, Jang MH (2015): Gadd45b Mediates Electroconvulsive Shock Induced Proliferation of Hippocampal Neural Stem Cells. *Brain Stimul*. 8:1021-1024.
57. Pusalkar M, Ghosh S, Jaggar M, Husain BF, Galande S, Vaidya VA (2016): Acute and Chronic Electroconvulsive Seizures (ECS) Differentially Regulate the Expression of Epigenetic Machinery in the Adult Rat Hippocampus. *Int J Neuropsychopharmacol*. 19.
58. Cao B, Luo Q, Fu Y, Du L, Qiu T, Yang X, et al. (2018): Predicting individual responses to the electroconvulsive therapy with hippocampal subfield volumes in major depression disorder. *Sci Rep*. 8:5434.
59. Cinar S, Oude Voshaar RC, Janzing JG, Birkenhager TK, Buitelaar JK, van den Broek WW (2010): The course of depressive symptoms in unipolar depressive disorder during electroconvulsive therapy: a latent class analysis. *J Affect Disord*. 124:141-147.
60. Drysdale AT, Grosenick L, Downar J, Dunlop K, Mansouri F, Meng Y, et al. (2017): Resting-state connectivity biomarkers define neurophysiological subtypes of depression. *Nat Med*. 23:28-38.
61. Redlich R, Opel N, Grotegerd D, Dohm K, Zaremba D, Burger C, et al. (2016): Prediction of Individual Response to Electroconvulsive Therapy via Machine Learning on Structural Magnetic Resonance Imaging Data. *JAMA Psychiatry*. 73:557-564.

Figure Legends

Figure 1 | **Differential effect of ECT on hippocampal volume and clinical outcome.** A, Scatter plot of volume change of the right hippocampus, computed as (posttreatment – pretreatment score)/pretreatment score x 100, versus number of ECTs; *n* = 241. Slope (controlling for number of ECTs squared, Age, Sex, Site, baseline depression score, and baseline hippocampal volume), 0.28 ± 0.08, (t(225) = 3.35, $p < 0.001$. B, Scatter plot of change in MADRS score, computed as pretreatment – posttreatment score, versus volume change of the right hippocampus; *n* = 248. Slope (controlling for Age, Sex, Site, baseline depression score and baseline hippocampal volume), -1.0 ± 0.35, t(233) = -2.84, $p < 0.005$. C, Boxplot comparing volume change of the right hippocampus in non-responders (MADRS reduction < 50%) versus responders (MADRS reduction > 50%), *n* = 248, t(234.13) = 2.62, $p = 0.009$. D, Scatter plot of change in MADRS score versus number of ECTs; *n* = 268. Slope (controlling for age, Sex and Site), - 0.28 ± 0.16, t(256) = -1.80, $p = 0.074$). Non-responders received more ECT sessions (13.2 ± 4.7 versus 11.5 ± 5.3, t(232.11) = 2.74, $p = 0.007$) than responders.

Figure 2 | **Effect of electrode placement on change in left and right hippocampal volume.** A. Changes in right hippocampal volume per number of ECT sessions for bilateral (BL, dashed line) and right unilateral (RUL, solid line) electrode placement. Both slope and change in volume was similar for BL and RUL ECT (slope: both ~.13; BL volume increase: 3.0 ± 1.7%, RUL volume increase: 2.7 ± 2.0%). B. Changes in left hippocampal volume per number of ECT sessions for BL (dashed line) and RUL (solid line) electrode placement. Slope was steeper and

volume change was greater for BL (slope: 0.18 ± 0.03; volume increase: 3.3 ± 2.2%) than RUL (slope: 0.06 ± 0.04; volume increase: 1.6 ± 2.1%) stimulation.

Characteristics of subjects	Mean	SD	n[#]
Controls			
Age	46.9	14.6	95
Baseline right hippocampal volume (mm^3)	4052.5	446.2	95
Change in right hippocampal volume (%)	0.05	0.8	95
Baseline left hippocampal volume (mm^3)	3948.0	444.3	95
Change in left hippocampal volume (%)	0.01	0.7	95
Baseline intracranial volume (cm^3)	1520.2	179.2	95
Patients			
Age	54.9	16.4	281
Baseline right hippocampal volume (mm^3)	3774.1	588.3	254[$]
Change in right hippocampal volume (%)	2.9	1.9	250[^]
Baseline left hippocampal volume (mm^3)	3657.9	561.0	254[$]
Change in left hippocampal volume (%)	2.2	2.3	250[^]
Baseline intracranial volume (cm^3)	1505.9	175.6	254[$]
Baseline depression score	33.3	8.2	279
Post treatment depression score	15.0	11.0	277
Duration of episode (months)	20.1	31.6	158
Number of ECTs, total	12.0	5.2	273[*]
Number of ECTs, BL only	14.6	7.5	50
Number of ECTs, RUL only	10.9	3.6	149
Number of ECTs, responders	11.5	5.3	166
Number of ECTs, non-responders	13.2	4.7	102

Table 1 The number of subjects ([#]) vary because of missing data for some variables. Information about number of ECTs ([*]) was missing for 8 subjects; some subjects received more than one form of lead placement and one subject also received LART stimulation. A total of 27 subjects ([$]) were missing MRI at either before or after treatment (baseline volume is not reported for these) and 4 subjects failed automated processing of volume change ([^]).

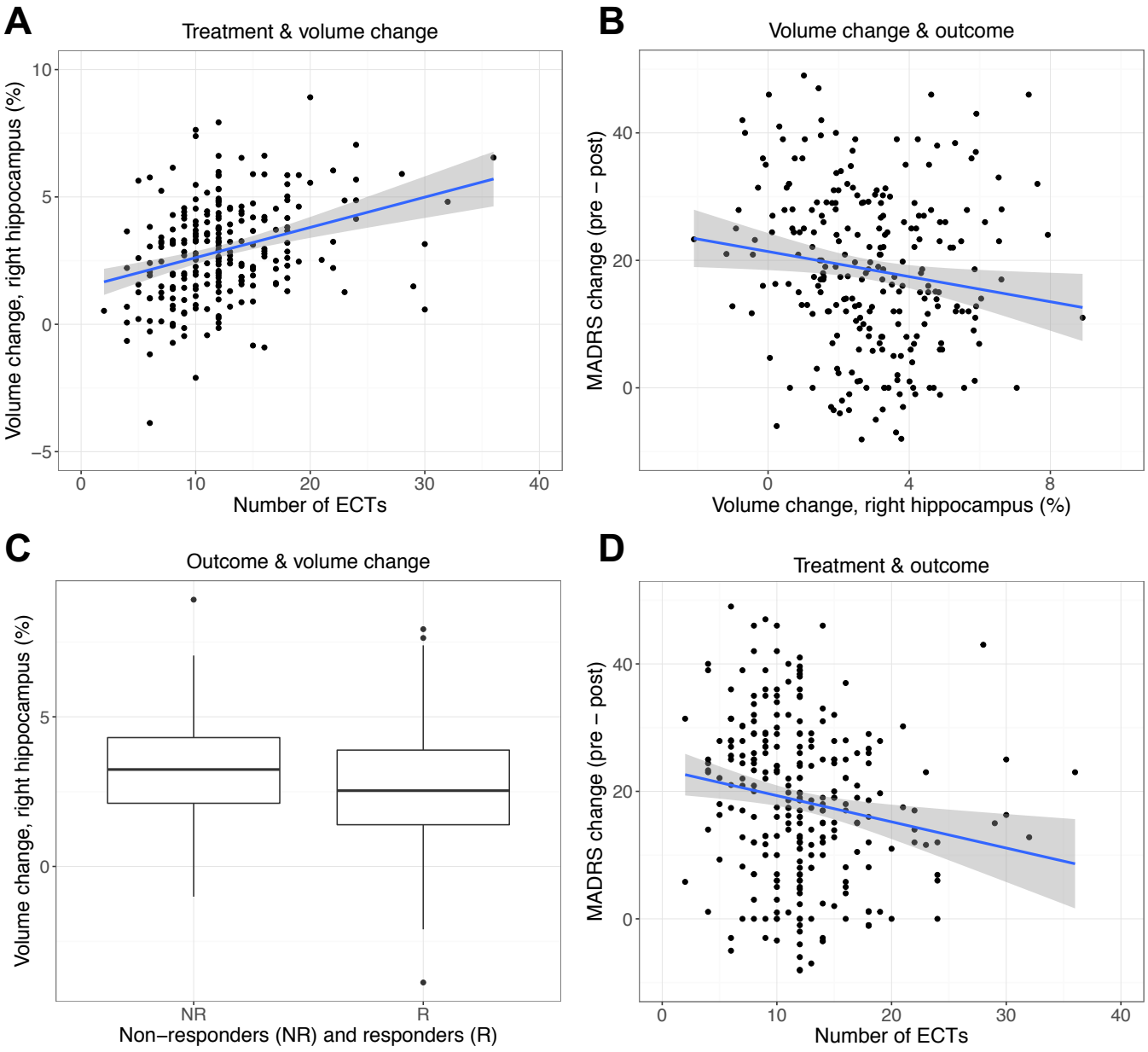
A
Treatment & volume change
Volume change, right hippocampus (%)
Number of ECTs
B
Volume change & outcome
MADRS change (pre – post)
Volume change, right hippocampus (%)
C
Outcome & volume change
Volume change, right hippocampus (%)
NR
R
Non–responders (NR) and responders (R)
D
Treatment & outcome
MADRS change (pre – post)
Number of ECTs

Figure 1

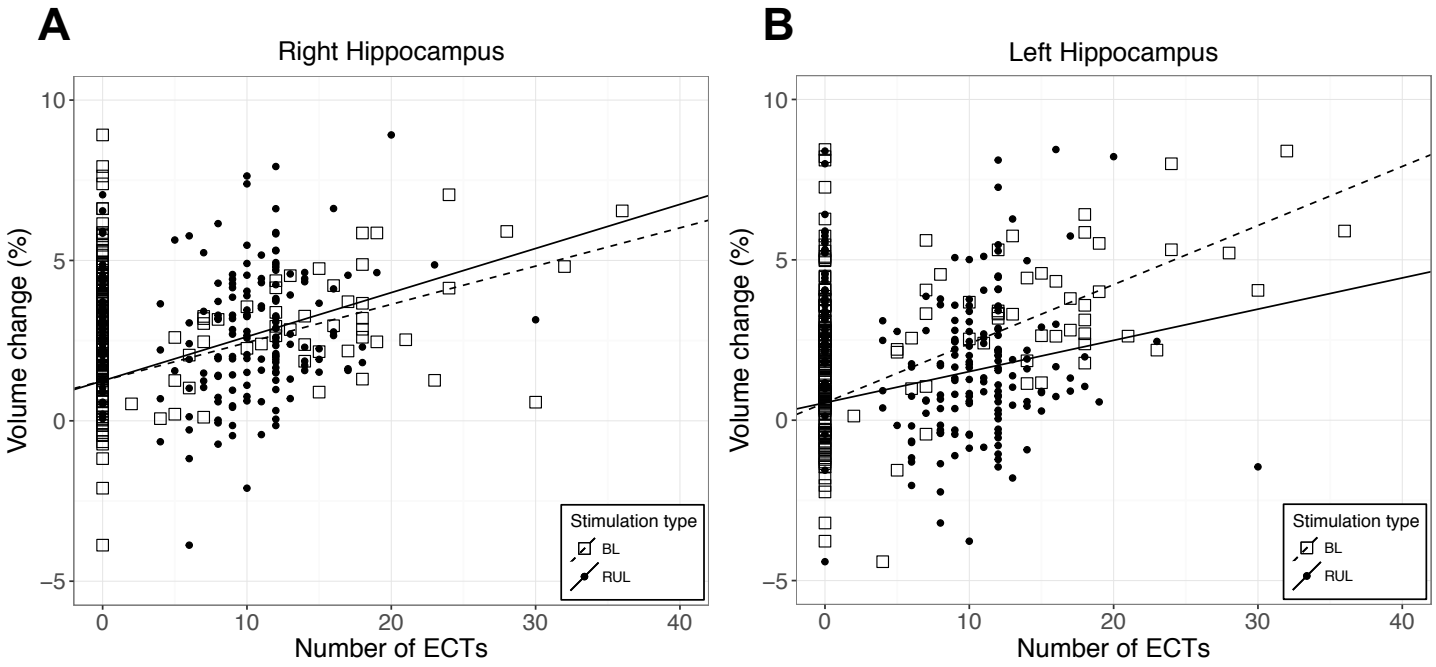
A
Right Hippocampus
Volume change (%)
Number of ECTs
Stimulation type
BL
RUL
B
Left Hippocampus
Volume change (%)
Number of ECTs
Stimulation type
BL
RUL

Figure 2

Volume of the Human Hippocampus and Clinical Response Following Electroconvulsive Therapy

Supplemental Information

Volume change and clinical outcome for the left hippocampus

Volume growth was associated with the number of ECT sessions for both the right (see main text) and the left hippocampus ($t(225) = 3.93$, $p < 0.001$). Controlling for the number of ECT sessions, relationships between change in clinical response and change in hippocampal volume were not significant for the right (see main text) or left hippocampus ($t(225) = -1.50$, $p = 0.14$).

Volume change for ECT responders and non-responders

Although the number of ECT sessions received for individual patients was confounded by the extent of their clinical response, understanding how clinical response relates to length of treatment provides further insight. Specifically, a model of change in MADRS score as a function of number of treatments showed a negative association $F(1,266) = 7.96$, slope = -0.41, $p = 0.005$, $R^2 = 0.03$ (Figure S1D), although after correcting for Age, Sex and Site this was not significant (slope = -0.28, $t(256) = -1.80$, $p = 0.074$). Hence, follow up analyses were performed to further clarify the effects of volume change and ECT session number in ECT responders and non-responders. First, we tested for the effect of response group (responder, non-responder) on hippocampal volume change, correcting for number of ECTs and number of ECTs squared, and found that the effect of group was not significant for the right (-0.35, $t(236) = -1.41$, $p = 0.16$), or the left (-0.50, $t(236) = -1.78$, $p = 0.08$) hippocampus (Figure S1A and B, respectively). Also, looking at responders separately from non-responders (Figure S1C and D) did not reveal positive relationships between volume change and clinical outcome (change in MADRS score) for the right or left hippocampus. Similarly, there was no positive association between number of ECTs and outcome for responders separated from non-responders (Figure S1E). Finally, to completely exclude variance associated with number of treatments, we used data from a subset of patients that received exactly 12 ECT sessions (the mode number of treatments). Again, a model of change in MADRS score as a function of volume change did not yield a significant relationship ($F(1,45) = 0.006$, $p = 0.94$, $R^2 = 0.0001$) (Figure S1F).

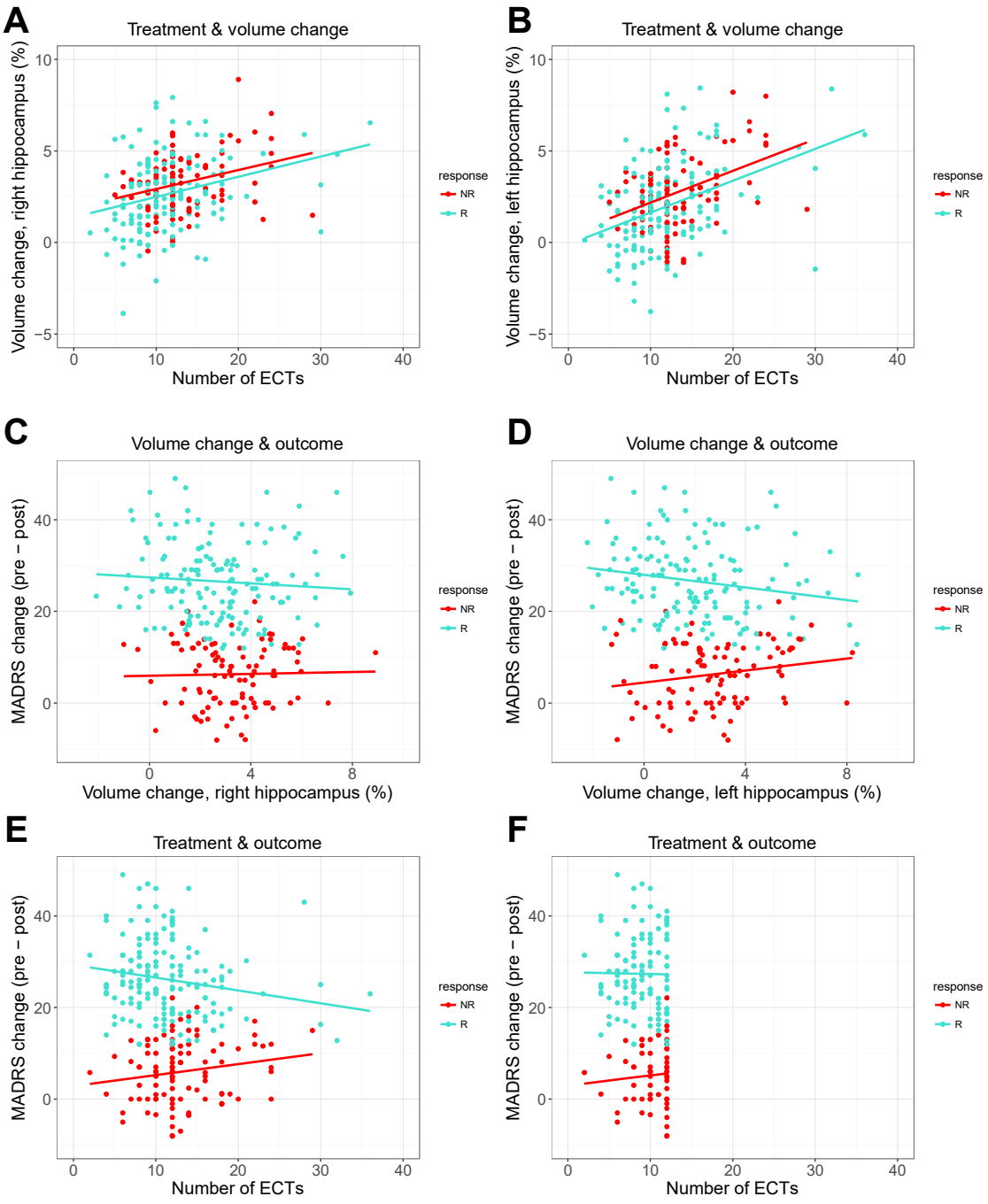

Figure S1. Effect of ECT on hippocampal volume and clinical outcome for responders and non-responders. A, Scatter plot of volume change for the right hippocampus versus number of ECTs in responders (blue) and non-responders (red); *n* = 241. B, Scatter plot of volume change for the left hippocampus versus number of ECTs in responders (blue) and non-responders (red); *n* = 241. C, Scatter plot of change in MADRS score versus volume change for the right hippocampus in responders (blue) and non-responders (red); *n* = 247. D, Scatter plot of change in MADRS score versus volume change for the left hippocampus in responders (blue) and non-responders (red); *n* = 247. E, Scatter plot of change in MADRS score versus number of ECTs in responders (blue) and non-responders (red); *n* = 267. F, Scatter plot of change in MADRS versus number of ECTs including patients only receiving ≤ 12 sessions classified as responders (blue) and non-responders (red); *n* = 171.

Supplementary Methods

Medications: Concurrent psychotropic medications were used at most sites, but there was virtually no change in medication during treatment (number of patients receiving each medication at baseline: antidepressants (*n* = 115), antipsychotics (*n* = 93), lithium (*n* = 0), other mood stabilizer (*n* = 35) or benzodiazepines (*n* = 56)). Information about dose was not available. Volume change of the right hippocampus did not differ between one site that tapered patients off all antidepressants, benzodiazepines and anticonvulsants (Figure S2) compared to all other sites (p = 0.27).

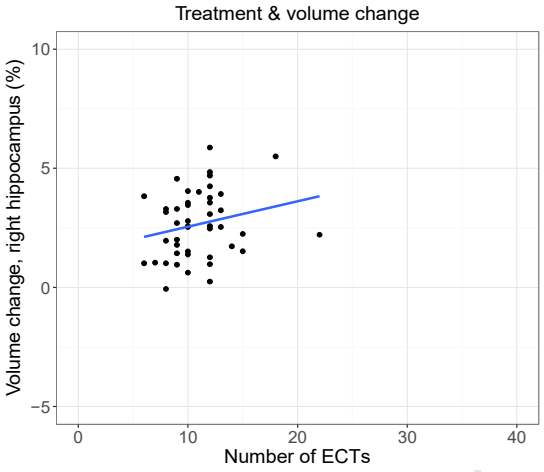

Figure S2. Scatter plot of volume change of the right hippocampus versus number of ECTs for the site that tapered patients off all medications before treatment. The mean volume change at this site was 2.6%, which did not differ from all other sites (2.9%), *p* = 0.27 *t*-test.

Electrode placement and clinical outcome: No significant difference for electrode placement was found when modelling separate slopes for RUL and BL stimulation (Figure S3).

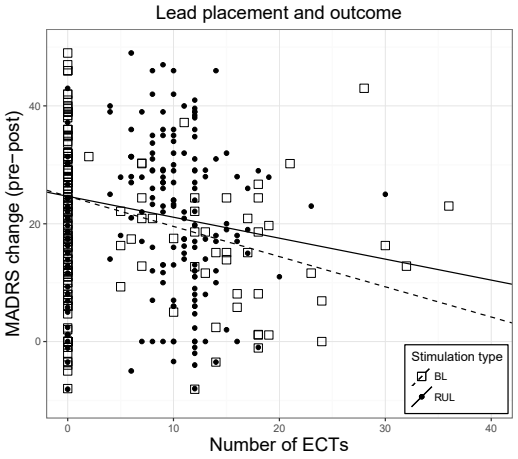

Figure S3. Treatment and clinical outcome for RUL and BL. Scatter plot of change in MADRS score versus number of ECTs for BL and RUL electrode placements. In a model with BL and RUL as separate predictors (controlling for age, sex, site, and baseline depression score), the slopes were -0.27 and -0.53 for BL and RUL stimulation, respectively. These slopes were not significantly different (*p* = 0.25, Linear Hypothesis test).

Supplementary results, complete statistical models

The full linear models for our main analysis are provided below. The model name corresponds to results presented in the Figures and in the main text.

Model 1a

Right hippocampus volume change ~ number of ECTs

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	2.991	1.516	1.973	0.050
number of ECTs	0.277	0.083	3.350	0.001
number of ECTs_sq	-0.005	0.002	-1.944	0.053
Age	-0.017	0.011	-1.541	0.125
Sex	-0.477	0.244	-1.955	0.052
Baseline MADRS	-0.024	0.015	-1.655	0.099
Baseline right hippocampus vol	0.000	0.000	-0.933	0.352
Site1	-0.641	0.452	-1.420	0.157
Site2	0.144	0.536	0.268	0.789
Site3	-0.454	0.533	-0.852	0.395
Site4	-0.050	0.447	-0.111	0.912
Site5	0.569	0.606	0.939	0.349
Site6	0.925	0.479	1.932	0.055
Site7	0.129	0.538	0.239	0.811
Site8	1.461	0.522	2.801	0.006

Model 1b

MADRS change ~ Right hippocampus volume change

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	-17.583	8.025	-2.191	0.029
Right hippocampus vol change	-0.996	0.350	-2.844	0.005
Age	0.127	0.063	2.010	0.046
Sex	-0.863	1.350	-0.639	0.523
Site1	8.669	2.537	3.418	0.001
Site2	6.831	2.959	2.308	0.022
Site3	8.623	4.318	1.997	0.047
Site4	4.048	2.862	1.414	0.159
Site5	3.987	2.480	1.608	0.109
Site6	5.874	3.338	1.760	0.080
Site7	7.915	2.744	2.884	0.004
Site8	4.104	2.890	1.420	0.157
Site9	11.341	3.006	3.773	0.000
Baseline MADRS	0.852	0.083	10.316	0.000
Baseline right Hippocampus vol	-0.001	0.001	-0.406	0.685

Model 1b including the number of ECT sessions

MADRS change ~ Right hippocampus volume change + num ECT

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	-15.141	8.135	-1.861	0.064
Right hippocampus vol change	-0.686	0.376	-1.826	0.069
Age	0.116	0.064	1.801	0.073
Sex	-0.216	1.391	-0.156	0.877
Site1	9.668	2.577	3.752	0.000
Site2	8.367	3.009	2.781	0.006
Site3	6.239	3.028	2.060	0.041
Site4	5.432	2.533	2.145	0.033
Site5	4.601	3.363	1.368	0.173
Site6	7.867	2.740	2.872	0.004
Site7	6.843	3.053	2.242	0.026
Site8	11.863	3.013	3.938	0.000
Baseline MADRS	0.879	0.084	10.484	0.000
Baseline right Hippocampus vol	0.000	0.001	-0.360	0.719
number of ECTs	-0.399	0.146	-2.737	0.007

Model 1d

MADRS change ~ Number of ECTs

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	16.242	3.705	4.384	0.000
Number of ECTs	-0.283	0.158	-1.796	0.074
Age	0.062	0.065	0.957	0.339
Sex	-0.542	1.493	-0.363	0.717
Site1	4.778	2.965	1.611	0.108
Site2	5.098	3.446	1.479	0.140
Site3	2.154	3.521	0.612	0.541
Site4	-2.224	2.881	-0.772	0.441
Site5	1.839	3.195	0.576	0.565
Site6	1.433	2.819	0.509	0.612
Site7	-3.663	3.222	-1.137	0.257
Site8	9.423	3.365	2.801	0.005

Model 2a

Right hippocampus volume change and lead placement

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	4.515	1.602	2.818	0.005
RUL	0.132	0.039	3.347	0.001
BL	0.127	0.032	4.012	0.000
Age	-0.017	0.012	-1.374	0.171
Sex	-0.433	0.272	-1.589	0.114
Site1	-0.872	0.530	-1.644	0.102
Site2	0.055	0.664	0.082	0.934
Site3	-0.577	0.782	-0.738	0.462
Site4	-0.168	0.524	-0.321	0.749
Site5	0.305	0.711	0.429	0.669
Site6	0.837	0.526	1.592	0.113
Site7	0.043	0.819	0.053	0.958
Site8	1.316	0.606	2.170	0.031
Baseline MADRS	-0.028	0.017	-1.678	0.095
Baseline right hippocampus vol	0.000	0.000	-1.242	0.216

Model 2b

Left hippocampus volume change and lead placement

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	3.966	1.816	2.184	0.030
RUL	0.061	0.042	1.461	0.146
BL	0.182	0.034	5.417	0.000
Age	-0.028	0.013	-2.053	0.042
Sex	-0.961	0.288	-3.338	0.001
Site1	-0.945	0.564	-1.675	0.096
Site2	-0.171	0.706	-0.242	0.809
Site3	-0.962	0.829	-1.161	0.247
Site4	0.358	0.553	0.647	0.518
Site5	0.358	0.754	0.475	0.636
Site6	0.703	0.558	1.262	0.209
Site7	0.046	0.868	0.054	0.957
Site8	1.249	0.643	1.941	0.054
Baseline MADRS	-0.023	0.018	-1.293	0.198
Baseline left hippocampus vol	0.000	0.000	-0.393	0.695

Model 2c

Volume change of left hippocmpus, Lead placement interaction

	Estimate	Std. Error	t value	Pr(>|t|)
(intercept)	2.097	2.137	0.981	0.328
number of ECTs	0.486	0.129	3.767	0.000
number of ECTs_sq	-0.008	0.003	-2.564	0.011
electrode placement (RUL)	0.258	1.093	0.236	0.814
Age	-0.027	0.013	-1.997	0.047
Sex	-1.069	0.288	-3.710	0.000
Site1	-0.965	0.558	-1.729	0.085
Site2	0.112	0.706	0.159	0.874
Site3	-1.671	0.971	-1.721	0.087
Site4	0.393	0.548	0.718	0.474
Site5	0.487	0.934	0.522	0.603
Site6	0.777	0.551	1.410	0.160
Site7	-0.627	0.973	-0.644	0.521
Site8	1.250	0.636	1.966	0.051
Baseline MADRS	-0.023	0.017	-1.325	0.187
Baseline left hippocampus vol	0.000	0.000	-0.292	0.771
number of ECTs : electrode placement (RUL)	-0.191	0.070	-2.736	0.007